



## Markers of bone and lipid metabolism with eslicarbazepine acetate monotherapy

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### ABSTRACT

**Objective:** To evaluate the impact of eslicarbazepine acetate (ESL) monotherapy on markers of bone and lipid metabolism.

**Methods:** We conducted a post-hoc analysis of data pooled from two Phase III, dose-blind, conversion-to-ESL (1600 mg and 1200 mg) monotherapy studies in patients with focal seizures. Laboratory measurements included lipids (total cholesterol [TC]; high-density lipoprotein cholesterol [HDL-C]; low-density lipoprotein cholesterol; and triglycerides) and markers of bone metabolism (alkaline phosphatase; 25-hydroxyvitamin D; osteocalcin; and parathyroid hormone [PTH]); measurements were taken at baseline, Week 18, and Month 12, and analyzed according to enzyme-inducing antiepileptic drugs (EIAEDs) use at baseline (+EIAED and -EIAED subgroups).

**Results:** Data from 337 treatment-compliant patients were used for the Week 18 analyses (+EIAED subgroup, n = 119; -EIAED subgroup, n = 218); data from 161 treatment-compliant patients were used for the Month 12 analyses (+EIAED subgroup, n = 53; -EIAED subgroup, n = 108). At baseline, alkaline phosphatase and PTH concentrations were higher in the +EIAED versus -EIAED subgroup. Changes from baseline in markers of bone turnover were generally insignificant, except for some elevation in alkaline phosphatase in the -EIAED subgroup (18 weeks and 12 months) and osteocalcin in both subgroups (18 weeks only). Regarding lipids, TC and HDL-C concentrations were higher in the +EIAED versus -EIAED subgroup at baseline. Concentrations of markers of lipid metabolism fell in the +EIAED group and rose in the -EIAED group, reaching very similar values that were intermediate between the -EIAED and +EIAED baseline values.

**Conclusions:** Based on this retrospective analysis, ESL seems to have had only a modest and primarily clinically insignificant impact on plasma lipids. More prospective data are needed to definitively ascertain the effects of ESL on bone metabolism.

### 1. Introduction

Carbamazepine (CBZ) has been a mainstay of epilepsy therapy since its introduction 50 years ago. Like phenytoin (PHT) and phenobarbital, however, its use is complicated by potent induction of the cytochrome P450 (CYP450) enzyme system. This leads to a number of metabolic effects, among them elevations in serum lipids (Bramswig et al., 2003;

Lopinto-Khoury and Mintzer, 2010) and alterations of bone metabolism (Brodie et al., 2013; Mintzer, 2010). The related compound oxcarbazepine (OXC) was subsequently developed, and appears to share some, though not all of the CYP450-inducing properties of CBZ; it does not appear to affect serum lipids in the same manner (Isojarvi et al., 1994), but it does have similar effects on bone metabolism (Mintzer et al., 2006).

**Abbreviations:** 25-OHD, 25-hydroxyvitamin D; AED, antiepileptic drug; CBZ, carbamazepine; CYP450, cytochrome p450; EIAED, enzyme-inducing antiepileptic drug; ESL, eslicarbazepine acetate; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; OLE, open-label extension; OXC, oxcarbazepine; PHT, phenytoin; PTH, parathyroid hormone; Q, quartile; QD, once-daily; TC, total cholesterol

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The most recent entrant into the dibenzazepine carboxamide class of drugs is eslicarbazepine acetate (ESL). ESL is an oral antiepileptic drug (AED) approved for the treatment of focal (partial-onset) seizures in patients  $\geq 4$  years of age. The approval of ESL was based, in part, on two Phase III studies that used a conversion-to-monotherapy study design (Jacobson et al., 2015; Sperling et al., 2015a).

Whether or not the induction of CYP450 by ESL leads to clinically relevant effects remains to be established. Concomitant ESL treatment is known to lower systemic exposure to simvastatin and, curiously, rosuvastatin (Gidal et al., 2017), which indicates that at least some enzymatic processes appear to be induced by the drug. A previous analysis suggested that, when used as adjunctive therapy, ESL had only a modest effect on serum lipids that was unlikely to be clinically meaningful (Mintzer et al., 2018b). To date, there are no published data relevant to the impact of ESL on bone metabolism.

We took advantage of the conversion-to-monotherapy design of the two ESL studies and their 12-month open-label extension (OLE) to perform a post-hoc analysis of the impact of ESL monotherapy on both plasma lipids and markers of bone metabolism. We separated the population into those switching from enzyme-inducing AEDs (EIAEDs) to ESL, and those switching from non-enzyme-inducing AEDs to ESL.

## 2. Material and methods

### 2.1. Study design

Studies 093-045 (NCT00866775) (Sperling et al., 2015a) and 093-046 (NCT01091662) (Jacobson et al., 2015) were randomized, dose-blind, conversion-to-monotherapy studies. The two studies were identical, and have been described in full elsewhere, including the study design, inclusion and exclusion criteria, and primary and secondary endpoints (Jacobson et al., 2015; Sperling et al., 2016, 2015a). As described by French et al., both studies used a historical control group for evaluation of efficacy (French et al., 2010). The studies were conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and all national, state, and local laws of the pertinent regulatory authorities. Approval was received from the relevant independent ethics committees/institutional review boards, and all patients provided informed consent.

Patients were aged 16–70 years with focal seizures not adequately controlled by one or two AEDs (only one sodium channel blocker was allowed). After an 8-week baseline period, patients were randomized in a 2:1 ratio to receive 1600 mg or 1200 mg ESL once-daily (QD) for 18 weeks (a 2-week ESL titration period, followed by a 6-week AED conversion period [other AEDs were withdrawn], and a 10-week ESL monotherapy period).

At the end of the dose-blinded period, eligible patients could enter a 12-month OLE study, 093-050 (NCT00910247) (Sperling et al., 2015b) during which they continued to receive open-label (OL) ESL. Doses could be adjusted at the discretion of the investigators, between 800 mg QD and 2400 mg QD, and patients were permitted to resume taking up to two concomitant AEDs, excluding OXC (in this article we report data from the OLE study only for those patients who continued to take ESL without adding other AEDs).

### 2.2. Laboratory measurements

Laboratory measurements were conducted in non-fasting conditions and included lipids (total cholesterol [TC]; high-density lipoprotein cholesterol [HDL-C]; low-density lipoprotein cholesterol [LDL-C]; and triglycerides) and markers of bone metabolism (alkaline phosphatase; 25-hydroxyvitamin D [25-OHD]; osteocalcin; and parathyroid hormone [PTH]).

Plasma concentrations of specified markers were determined at baseline, after 18 weeks of dose-blind treatment, and after 12 months of OL treatment.

### 2.3. Analyses

Analyses of data from the dose-blind treatment period were conducted for the pooled population of compliant patients. Analyses of data from the OLE study were conducted for patients compliant for the 12-month OL period and who continued to take ESL monotherapy without adding other AEDs, i.e., ‘true monotherapy’ patients. Patients who took  $\geq 70\%$  of their ESL doses were deemed to be compliant.

Summary statistics were calculated for subgroups defined retrospectively on the basis of whether or not patients were taking EIAEDs (CBZ or PHT) during the baseline periods of Studies 045 and 046. CBZ and PHT were specified as EIAEDs for this analysis, as they were the most frequently used EIAEDs in the two studies. The + EIAED subgroup included patients taking an EIAED at baseline; the –EIAED subgroup included patients not taking an EIAED at baseline.

Exploratory, post-hoc, nonparametric Wilcoxon signed-rank tests were conducted to compare markers of lipid metabolism and bone turnover between baseline and 18 weeks, and between baseline and 12 months (separately for the + EIAED and –EIAED groups), as it cannot be assumed that the data were normally distributed. Fisher’s exact tests were conducted to compare proportions of clinically meaningful changes from baseline in lipid parameters between the + EIAED and –EIAED groups at 18 weeks and 12 months.

## 3. Results

### 3.1. Patient demographics and baseline characteristics

#### 3.1.1. Dose-blind treatment

Of the 365 patients who received at least one dose of ESL (1600 mg or 1200 mg), 337 (92%) were treatment compliant. Of the compliant patients, 119 (35%) were using an EIAED (CBZ or PHT) during the baseline period (+ EIAED subgroup) while 218 (65%) were not using an EIAED during baseline (–EIAED subgroup). Median age (range) was 38 (16–68) years and 48% of patients were male.

#### 3.1.2. Open-label treatment

A total of 274 patients entered the OLE study. By the cut-off date for this analysis (March 21, 2014), 180 patients had completed a year of OL treatment and 157 had completed a year of ESL monotherapy (without reintroducing other AEDs); 161 patients were treatment compliant. Of the compliant patients, 53 (33%) were in the + EIAED subgroup and 108 (67%) were in the –EIAED subgroup.

In the + EIAED subgroup, the most frequently used baseline AEDs were CBZ (77%) and PHT (24%). Levetiracetam (34%), valproic acid (27%), and lamotrigine (26%) were the most frequently used baseline AEDs in the –EIAED subgroup.

Rates of use of concomitant medications with potential to alter markers of bone turnover differed between the + EIAED and –EIAED subgroups with respect to bisphosphonates, calcium, and vitamin D (when combined into a single group) and OXC (Table 1). OXC was used by 10% of patients in the –EIAED subgroup and 1% in the + EIAED subgroup, while bisphosphonates, calcium, or vitamin D were used by 22% of patients in the –EIAED subgroup and 11% in the + EIAED subgroup.

### 3.2. Markers of bone turnover

At baseline, mean alkaline phosphatase ( $p = 0.000$ ) and parathyroid hormone ( $p = 0.022$ ) concentrations were higher in the + EIAED subgroup than the –EIAED subgroup, while 25-OHD and osteocalcin were not different ( $p > 0.05$ ; Fig. 1). After conversion to ESL monotherapy, changes at both 18 weeks and 12 months were primarily associated with  $p$ -values  $> 0.05$ , except for some elevation of alkaline phosphatase in the –EIAED subgroup after switch, consistent with some degree of enzyme induction (Fig. 1). In addition, there was an increase

**Table 1**

Baseline use of medications with known potential to alter markers of bone turnover, according to use of EIAEDs at baseline<sup>a</sup>.

Concomitant drug, n (%)	-EIAED n = 218	+EIAED n = 119
Bisphosphonates	2 (0.9)	1 (0.8)
Calcium	24 (11.0)	9 (7.6)
Vitamin D	24 (11.0)	8 (6.7)
Bisphosphonates, or calcium, or Vitamin D	48 (22.0)	13 (11.0)
OXC	21 (9.6)	1 (0.8)
Statins <sup>b</sup>	27 (12.4)	12 (10.1)

-EIAED/+EIAED, patients not taking/taking EIAEDs during baseline; OXC, oxcarbazepine.

Data are numbers and percentages of patients in each subgroup of the dose-blind studies who were taking medications of each type during baseline (only medications with known potential to alter markers of bone turnover are listed).

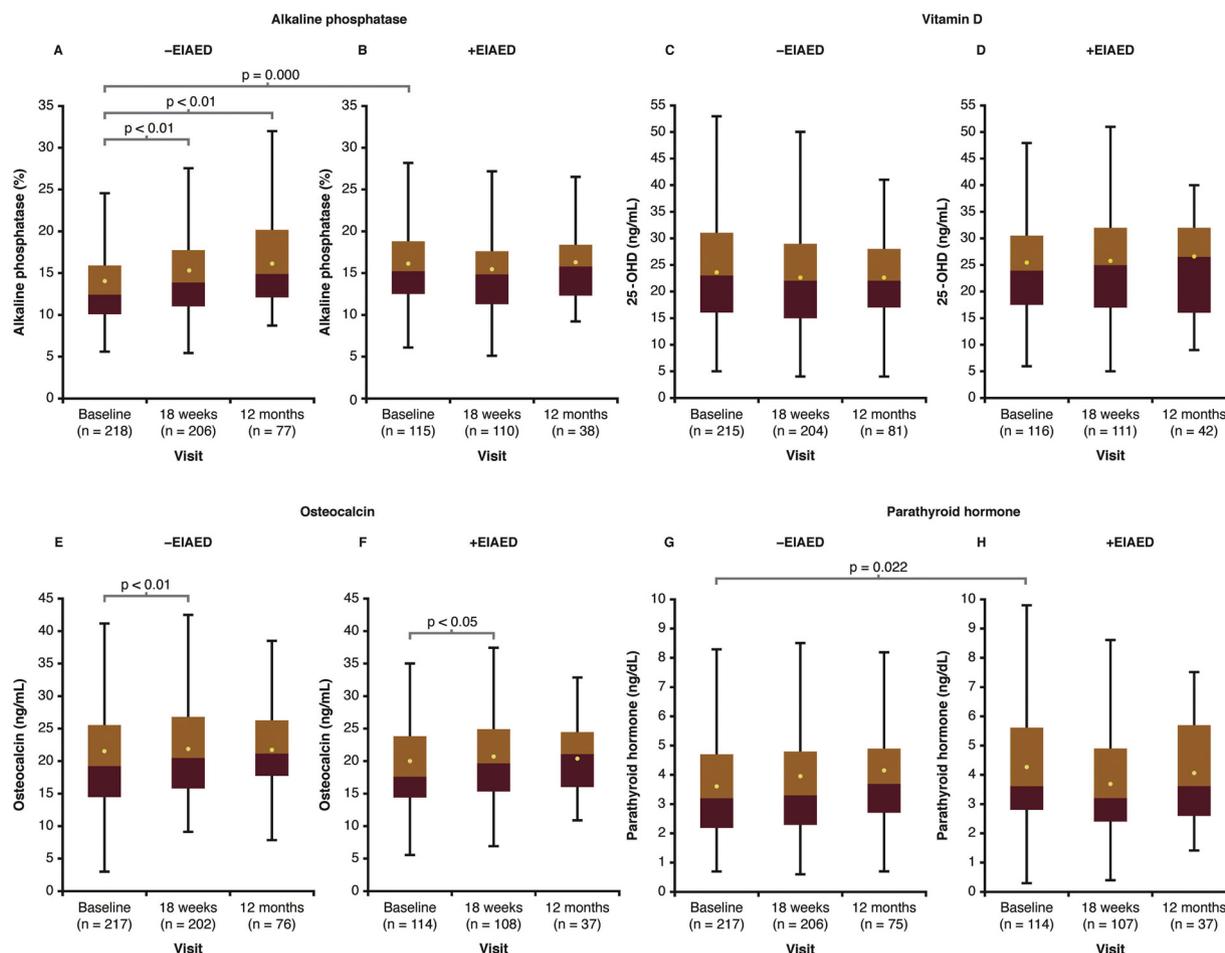
<sup>a</sup> Compliant patients only i.e., those who took  $\geq 70\%$  of their ESL doses.

<sup>b</sup> Simvastatin, atorvastatin, pravastatin, rosuvastatin, lovastatin, or fluvastatin.

in osteocalcin between baseline and 18 weeks (but not 12 months) in both the -EIAED and +EIAED subgroups, also potentially consistent with some degree of enzyme induction.

**3.3. Markers of lipid metabolism**

At baseline, concentrations of all evaluated markers of lipid metabolism were higher in the +EIAED subgroup than the -EIAED subgroup, with  $p$ -values  $< 0.05$  for TC ( $p = 0.002$ ) and HDL-C ( $p = 0.016$ ) (Fig. 2). After 18 weeks and 12 months of ESL monotherapy, concentrations of all lipid markers fell in the +EIAED group and rose in the -EIAED group; TC concentrations reached very similar mean values that were intermediate between the -EIAED (188.5 mg/dL) and +EIAED (206.4 mg/dL) baseline values (Fig. 2).  $P$ -values were  $< 0.05$  for the majority of cholesterol measures (though not for triglycerides, or for LDL-C in the +EIAED subgroup).



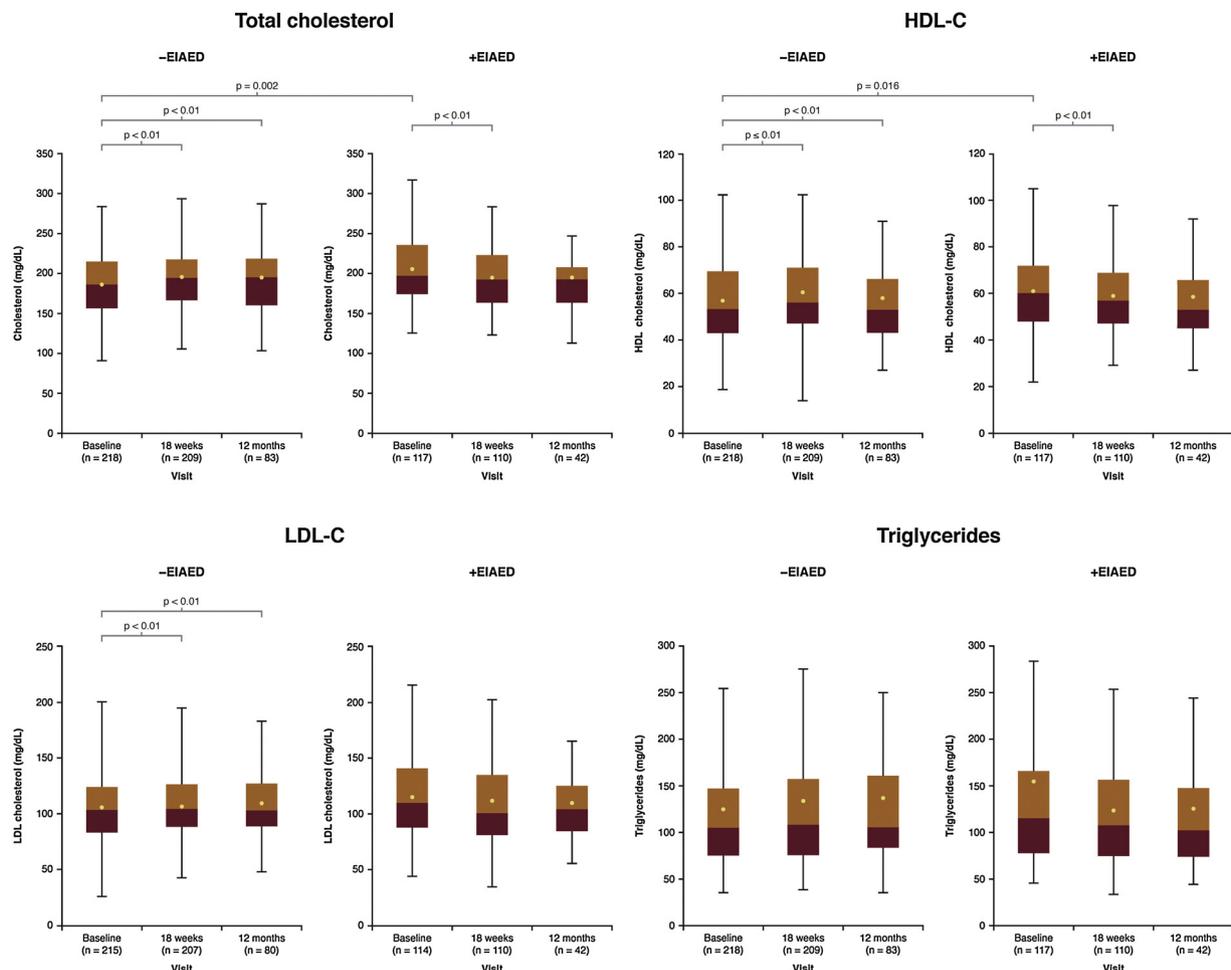
**Fig. 1.** Markers of bone turnover at baseline and after 18 weeks and 12 months of ESL monotherapy, according to use of EIAEDs at baseline.

The division between the top and bottom of the box represents the median value (i.e., the 50th quartile) and the yellow dot represents the mean value; the top of the box represents the 75th quartile, and the bottom of the box the 25th quartile. The upper and lower ends of the whisker represent the maximum and minimum values, respectively (excluding outliers). Values  $< Q1 - 1.5x IQR$  or  $> Q3 + 1.5x IQR$  were considered outliers ( $Q1$  is the 25th quartile,  $Q3$  is the 75th quartile, and  $IQR = Q3 - Q1$ ); values ranged from 5.1 to 95.6% for alkaline phosphatase, 4–83 ng/mL for 25-OHD, 3.0–95.2 ng/mL for osteocalcin, and 0.3–13.7 ng/dL for PTH. BL data are the last non-missing values prior to initiation of study medication.

Patients receiving OL treatment did not take other AEDs.

$P$ -values were calculated using the Wilcoxon signed-rank test to test whether the difference in values between baseline and each visit (18 weeks or 12 months) was equal to 0 in the -EIAED or +EIAED subgroups, and to test whether mean baseline values differed between the -EIAED or +EIAED subgroups (all  $p$ -values are nominal, being uncorrected for multiplicity).

25-OHD, 25-hydroxyvitamin D; BL, baseline; +EIAED, taking enzyme-inducing antiepileptic drugs during baseline; -EIAED, not taking enzyme-inducing antiepileptic drugs during baseline; ESL, eslicarbazepine acetate; IQR, interquartile range; OL, open-label; PTH, parathyroid hormone; Q, quartile.



**Fig. 2.** Markers of lipid metabolism at baseline and after 18 weeks and 12 months of ESL monotherapy, according to use of EIAEDs at baseline.

The division between the top and bottom of the box represents the median value (i.e., the 50th quartile) and the yellow dot represents the mean value; the top of the box represents the 75th quartile, and the bottom of the box the 25th quartile. The upper and lower ends of the whisker represent the maximum and minimum values, respectively (excluding outliers). Values  $< Q1 - 1.5 \times IQR$  or  $> Q3 + 1.5 \times IQR$  were considered outliers (Q1 is the 25th quartile, Q3 is the 75th quartile, and  $IQR = Q3 - Q1$ ); values ranged from 90 to 444 mg/dL for TC, 14–153 mg/dL for HDL-C, 31–328 mg/dL for LDL-C, and 33–2081 mg/dL for triglycerides. BL data are the last non-missing values prior to initiation of study medication.

Patients receiving OL treatment did not take other AEDs.

P-values were calculated using the Wilcoxon signed-rank test to test whether the difference in values between baseline and each visit (18 weeks or 12 months) was equal to 0 in the -EIAED or +EIAED subgroups, and to test whether mean baseline values differed between the -EIAED or +EIAED subgroups (all p-values are nominal, being uncorrected for multiplicity).

BL, baseline; +EIAED, taking enzyme-inducing antiepileptic drugs during baseline; -EIAED, not taking enzyme-inducing antiepileptic drugs during baseline; ESL, eslicarbazepine acetate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; OL, open-label; Q, quartile; TC, total cholesterol.

#### 4. Discussion

The chief finding of this investigation is that plasma lipids fell when patients were converted from EIAEDs to ESL, but rose in those converted from non-inducing AEDs to ESL. This suggests that at the doses tested, the enzyme-inducing effect of ESL may differ from that of the AEDs to which patients were exposed at baseline.

Changes from baseline in cholesterol and its fractions were largely associated with p-values  $< 0.05$ . The fact that this was not the case for triglycerides may well be a function of the substantial variability of this measure, a factor also seen in other studies (Nishiyama et al., 2019). In addition, these measurements were made non-fasting; recent evidence indicates that this has minimal impact on cholesterol measures, but it can certainly affect triglycerides (Dyce, 2018; Nordestgaard, 2017).

Assessing the clinical significance for these data is interesting. It is perhaps instructive to view each of the lipid measures as a three-way comparison: the baseline value in the non-inducing AED group,

presumably reflecting the ‘normal’ state of patients’ cholesterol production; the baseline value in the +EIAED group, presumably reflecting the effect of full-fledged inducers; and the value (for either group) after being switched to 1200/1600 mg ESL monotherapy, presumably reflecting the impact of the latter drug. The fact that the post-baseline values were so similar in the two groups reinforces the utility of this comparison. Thus, for TC, one might infer that a mean baseline value of 188 mg/dL (non-inducer) was increased by about 18 mg/dL with the use of CBZ or PHT (to 206 mg/dL, the baseline +EIAED value; Fig. 2); this is consistent with prior work (Bramswig et al., 2003; Mantel-Teeuwisse et al., 2001; Mintzer, 2010; Yilmaz et al., 2001). With ESL, it increased only by about 7 mg/dL (to 195 mg/dL, the 12 month value in the -EIAED subgroup). While the effect of ESL on TC was consistent enough to yield a p-value  $< 0.05$ , this is clearly not a large enough effect to be considered clinically meaningful. This is quite similar to what was seen in an investigation of lipids in the ESL adjunctive studies (Mintzer et al., 2018b). Overall, our findings here,

reinforced by the prior study, suggest that ESL did not have a clinically important impact upon plasma lipids in the majority of patients.

Our findings with respect to bone metabolism are less clear. The lack of significant change in bone metabolic markers may simply indicate that ESL has little or no meaningful effect on these. However, the baseline data, before the switch to ESL, are themselves unusual in that there was no difference in 25-OHD between the two groups, despite a large body of evidence indicating that CBZ can reduce 25-OHD substantially (Mintzer, 2010; Mintzer et al., 2006). This makes it difficult to interpret the lack of change in 25-OHD levels subsequent to the switch to ESL. The reason for the lack of baseline difference in this measure is unclear; it is not likely to be related to Vitamin D supplementation, nor to calcium supplementation, since this was seen at comparable rates in both groups.

With regard to the bone turnover markers, the raw numbers in the -EIAED subgroups for both alkaline phosphatase and PTH settled at values similar to the + EIAED baseline after 12 months of switching to ESL; however, the increase from baseline was associated with a  $p$ -value  $< 0.05$  only for alkaline phosphatase. This suggests the possibility that ESL might increase bone turnover; however, the  $p$ -value associated with changes from baseline in PTH was  $> 0.05$  and there was no difference between osteocalcin and 25-OHD at baseline, making this far from clear. More prospective work needs to be done to clarify the impact of ESL on bone metabolism.

There are a number of limitations of this work. As is typical for a post-hoc analysis, there were several potentially important factors for which we could not entirely account. With respect to lipids, some patients were also taking 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (-EIAED subgroup, 12%; +EIAED subgroup, 10%). However, the lipid-lowering effect of these agents also appears to be impacted by EIAEDs (Gidal et al., 2009; Mintzer et al., 2018a) and not by ESL (which appears to have only a pharmacokinetic, not a pharmacodynamic, interaction with HMG-CoA reductase inhibitors) (Gidal et al., 2017; Mintzer et al., 2018b), so that one would expect the same direction of lipid changes when EIAEDs are replaced by ESL. The similarity of our lipid data to other published work also suggests that this may not have been a major factor in our findings. Having obtained our measurements in the non-fasting state makes the triglyceride data less reliable. Regarding the bone markers, the fact that some patients were supplementing with bisphosphonates, calcium, or Vitamin D is a potential confounder, and more patients were taking these concomitants in the -EIAED subgroup than in the + EIAED subgroup. OXC was also used in more patients in the -EIAED versus the + EIAED subgroup. We were also unable to ascertain menopausal status for the female subjects, which could certainly have impacted bone metabolism, and did not adjust to account for patients taking oral contraceptives. However, we do not believe that oral contraceptives have sufficient impact on bone metabolism to have substantially affected the results (Tremolieres, 2013).

An important limitation to this analysis is that Wilcoxon signed-rank tests were neither pre-planned nor adjusted for multiplicity, and thus the calculated  $p$ -values are nominal only. In addition, although  $p$ -values  $< 0.05$  are widely used to measure statistical significance in medical literature, they should not be over-interpreted in this manuscript. Differences with  $p$ -values  $< 0.05$  were more frequent in the -EIAED subgroup than in the + EIAED subgroup, likely because there were almost twice the number of patients in the former. For a given observed difference, a bigger sample size tends to be associated with a smaller  $p$  value, because the  $p$ -value is, in part, a function of sample size. For example, in the -EIAED group, differences in LDL-C between baseline (104 mg/dL) and 18 weeks (105 mg/dL), as well as 12 months (103.5 mg/dL), were associated with  $p$ -values  $< 0.01$  (Fig. 2). By comparison, in the + EIAED group, differences between baseline (110 mg/dL) and 18 weeks (101 mg/dL), as well as 12 months (103 mg/dL), were associated with  $p$ -values higher than 0.05, even though differences were numerically higher in the + EIAED group (Fig. 2). A

clinically meaningful difference may not be statistically significant at the 5% level due to a small sample size; the reverse could also be true.

In summary, based on this retrospective analysis, ESL seems to have had only a modest and primarily clinically insignificant impact on plasma lipids. More prospective data are needed to definitively ascertain the effects of ESL on bone metabolism.

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## Data sharing statement

Sunovion Pharmaceuticals Inc. is part of a clinical trial data sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data. For up-to-date information on data availability please visit: <https://www.clinicalstudydatarequest.com/Study-Sponsors.aspx> and click on Sunovion.

## Declaration of Competing Interest

Scott Mintzer reports receiving honoraria from UCB, Greenwich Biosciences, and Eisai; and receiving a research grant from UCB. Tawnya Constantino reports receiving honoraria from Sunovion Pharmaceuticals Inc. Barry Gidal reports advisory council/committee membership for Eisai, Sunovion Pharmaceuticals Inc., and GW Pharma; receiving honoraria from Eisai, Sunovion Pharmaceuticals Inc., and Greenwich; and receiving grants or funds from UCB. Parul Bhargava, Todd Grinnell, and David Blum report employment with Sunovion Pharmaceuticals Inc.

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